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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/071,648	02/11/2002	Daniel Djakiew	P 0280704 DJDA421003	1853

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EXAMINER	
PRIEBE, SCOTT DAVID	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/071,648	DJAKIEW, DANIEL	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *19-27 and 29-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 June 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-18 and 28 in the paper filed 12/22/03 is acknowledged. The traversal is on the ground(s) that examination of groups O, II, III, VI, and VIII would not constitute an undue burden. Applicant also argues that claim 2 requires measurement of p75 mRNA, as in Group VI. However, claim 2 recites no such requirement. This is not found persuasive because these inventions have acquired separate status in the art, as shown by their classification, and would therefore require different searches based upon that different status. The search of group VI would not be required for groups I-III or VIII, and *vice versa,* nor would the search of group VIII be required for groups I-III, nor would the search of groups II and III be required for group I. Consequently, at least a burden of search would be imposed. With respect to claims 19, 22, 28 and 29, claim 28 was inadvertently omitted from group I. Claims 19, 22, and 29 were omitted from groups because they are claims linking independent or distinct inventions, as indicated on page 4 of the preceding Office action.

The requirement is still deemed proper and is therefore made FINAL.

Claims 19-27 and 29-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper filed 12/22/03.

Claim Objections

Claims 1-18 and 28 are objected to because of the following informalities: Claims 1 and 28 each recite "administering to the subject $p75^{NTR}$ gene". This is improper grammar. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting prostate tumor growth comprising direct or local administration to the prostate tumor of a nucleic acid comprising coding sequence for full-length p75 protein, lacking the 3' terminal 1800-1900 nucleotides of the 3' UTR of the p75 gene, under control of sequences required for its expression in prostate tumor cells, does not reasonably provide enablement for preventing prostate tumor metastasis, treating other types of cancer, all routes of delivery, or all fragments of a p75 gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention is broadly directed to a method for treatment or prophylaxis of any cancer in any subject in need thereof by administration, by any route, of a "$p75^{NTR}$ gene or fragment thereof," in an amount effective to increase tumor suppression or tumor apoptosis. The claims do not require that the p75 protein be expressed from the gene or fragment. Claims 10-18

and 28 are limited to treatment of prostate tumors. The specification lacks any working example of the claimed method. The experimental results disclosed are directed to establishing that p75 functions as a tumor suppressor in prostate cells, but do not present a test of the method itself. The mouse model described involved ectopic implantation of selected human prostate tumor cells that had been transfected with a vector expressing p75 at various levels. This model represents an idealized situation in which all tumors cells in a subject would be transfected with a gene therapy vector. Even so, the results presented in the specification (Fig. 3) show that increasing expression of p75 slows but does not halt tumor growth. As discussed more fully below, transfection of all tumor cells is far from what was (and is) achievable in cancer gene therapy.

Claims 1-9 embrace treating any type of cancer. The instant invention appears to be based upon the finding that $p75^{NTR}$ is a tumor suppressor in prostate tissue. The specification provides no evidence that any other type of cancer involves loss of p75 expression, nor is there any evidence of record from the prior art. Para. 74 of the specification indicates that A875 human melanoma, for example, overexpresses p75. Therefor, increasing expression of p75 in melanoma would not be expected to increase growth suppression or apoptosis as required by these claims. In the absence of any teachings in the specification or the prior art of record that p75 would act as a tumor suppressor for any type of tumor than prostate tumors, and the finding that it is not a tumor suppressor in melanoma, the suitability of the claimed method for treating other types of cancer is unpredictable, and would require further investigation involving trial and error experimentation to determine other "subjects in need thereof."

The claims recite administering a "$p75^{NTR}$ gene or fragment thereof". The gene would be that found in the genome of a cell, and would at least contain introns and transcribed 5'- and 3'-untranslated regions. The specification teaches that the p75 promoter is constitutive, the p75 gene is intact and transcribed in prostate cancer cells. The experiments described in the specification involved expression of p75 from a p75 cDNA, not a p75 gene. Since the cDNA lacks introns, it is not a fragment of the p75 gene. In para. 75, the specification discloses that if prostate cancer cells are transfected with the complete cDNA, including the full 3'-UTR, no appreciable expression of p75 is observed, similar to expression from the intact p75 gene present in the prostate cancer cell lines. Since the intact full length gene of the prostate cancer cells is unable to express appreciable p75, it is unlikely that administration of the full length p75 gene would increase tumor suppression or apoptosis of tumor cells as required by the claims. The specification teaches that most of the 3'-UTR was deleted, leaving only 100-200 nucleotides, in order to obtain appreciable expression of p75. Transfection of prostate tumor cells with a full length cDNA failed to yield significant expression of p75 protein. The specification suggests that instability of the mRNA is responsible for the decreased expression in prostate cancer cells. The specification fails to identify which part of the 3' UTR is responsible for the instability. The specification suggests that agents which stabilize the mRNA might overcome the instability. However, the specification does not identify any specific agents that would stabilize the p75 mRNA, nor is there any evidence of record that such agents were known in the prior art. Thus, one of skill in the art would have to engage in trial and error experimentation in order to identify such agents, in the absence of any meaningful guidance as to what types of compounds might be effective.

As written, the claims do not require that the p75 gene transfect tumor cells, or that it be expressed in tumor cells. As written, the claim language implies simply that administration of the p75 gene is required to promote tumor suppression or apoptosis. However, the experimental results presented in the specification show that it is expression of p75 protein in prostate tumor cells that results in tumor suppression and apoptosis, not the mere presence of the gene in the tumor cell, which is intact in the tumor cell lines examined, or presence or expression of the gene elsewhere in the body of the subject. Consequently, embodiments of the invention as claimed where the p75 gene is not delivered to and taken up specifically by tumor cells or is not expressed in tumor cells, e.g. because it lacks the requisite transcriptional regulatory sequences, would be inoperative.

Also, "a fragment" of a p75 gene also reads on sequences lacking all or some p75 coding sequence. The specification (last line) indicates that the fragment should be "capable of promoting $p75^{NTR}$ expression," but it is unclear exactly what this means. It could mean that the fragment should encode full length p75 protein, or it could mean a p75 promoter sequence, which promotes p75 expression in nature. The specification provides no teaching that the fragment could encode less than all of p75. At a minimum, the claims should be limited to administering a p75 cDNA comprising only the first 100-200 nucleotides of the 3' UTR (or a comparable alternative limitation).

The claims broadly permit any route of administration of the p75 gene, claim 28 is directed in part to preventing prostate tumor metastasis. Gomez-Navarro et al. (Eur. J. Cancer 35 (6) : 867-885, Jun. 1999) reviews the state of cancer gene therapy before the instant invention was made. The instant invention falls into the general strategy of mutation compensation, which

includes treatment with vectors expressing tumor suppressors and promoters of apoptosis. The reference indicates that gene therapy for delivery of p53, RB1 and BRCA1 were being studied in human clinical trials. The reference discloses that even after delivery of tumor suppressor genes, some tumors show persistent tumorogenicity and proliferation, a major obstacle for tumor suppressor gene therapy (page 869, col. 1). With respect to modulating apoptosis in tumor cells, the reference discloses that "current vectors are far from achieving *in vivo* the requisite high levels of tumour cell modification," and that the complexity and redundancy of signaling circuits involved in apoptosis may require modulation of several components to provoke apoptosis *in vivo* (page 871, col. 2). The reference points out that because mutation compensation strategies modulate intracellular responses, that nearly all tumor cells would have to be transfected to be clinically effective, and that the current state of development of gene therapy vectors, both viral and non-viral, makes this feat unachievable within non-toxic margins of vector dose" (page 871, col. 2; page 875, col. 1). Consequently, quantitative transduction into tumor cells by *in situ* administration may be essential (page 875, col. 1). Table 5 of Gomez-Navarro briefly summarizes advantages and disadvantages of various vector systems, notably non-viral delivery suffered from inefficient delivery and transient expression, retroviral vectors are unstable *in vivo,* and adenoviral vectors induce potent immune response. Meng et al. (Chapter 1, Gene Therapy of Cancer, pp. 3-20, 1999) in reviewing tumor suppressor gene therapy discloses that while intratumoral administration assures delivery to the tumor, intravascular and intracavitary delivery present significant physical barriers to efficient delivery. The specification mentions using vector systems that incorporate ligands for targeting specific cellular receptors, but fails to identify any such targeting ligands for tumor cells in general, or prostate tumors specifically, nor is there any

evidence of record that such tumor cell specific targeting ligands were known in the art. The instant specification does not disclose any advances in vector design or delivery, rather the specification teaches using those vector systems Gomez-Navarro indicates were currently inadequate, and indicates that any route of administration could be used, in contrast to the teachings in the art.

Tait et al. (Clin. Cancer Res. 5: 1708-1714, July 1999) presents results from halted clinical trials for treatment of epithelial ovarian cancer with a retroviral vector expressing BRCA1. The vector was delivered locally or semi-locally by intraperitoneal injection to patients having advanced stage epithelial ovarian cancer (Phase I trials) or with minimal or recurrent epithelial ovarian cancer (Phase II). In the Phase I trial, the vector was stable, and the treatment produced minimal immune response to the vector and was found to be partly effective against small tumors (<2 mm) in some patients, but ineffective against large tumors. In contrast, treatment of patients in Phase II was accompanied unexpectedly by rapid and robust development of neutralizing antibodies and degradation of the vector, and was completely ineffective against the tumors (<2 mm). The authors described this result as a "therapeutic quagmire". (See Abstract and Discussion for overview).

As mentioned above, the specification presents results for a mouse model where all tumor cells had been transfected with a p75 gene, which as indicated in Gomez-Navarro is unachievable with current vector technology. Despite all tumor cells expressing exogenous p75, the ectopic tumors continued to grow, even in the case of high p75 expression. Given this result and the teachings in the prior art regarding the inability of extant vector systems to transfect

sufficient tumor cells, it is not credible that the claimed method would succeed in "preventing" prostate tumor metastasis, as in claim 28.

Therefore, in light of the disparity between breadth of the claims and the specific guidance in the specification regarding the types of cancer which can be treated and the scope of a "$p75^{NTR}$ gene or fragment thereof" and ancillary sequences required for expression of p75, the disparity between the breadth of the claims and the state of the prior art regarding effective routes of administration, the overall unpredictability of gene therapy and current barriers for effective gene delivery illustrated by the prior art, the lack of relevant and comparable working examples, and the amount of experimentation required to develop effective vector systems, it would require undue experimentation to practice the invention as broadly as claimed.

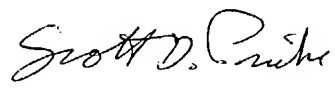
Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 6 is directed to an embodiment of the claimed invention where a "tumor cell apoptosis promoting agent" is administered in addition to the p75 gene. This agent is described only in terms of its function. The specification provides no examples of such agents, and no physical description of what such agents actually are. Consequently, there is no evidence in the specification that applicant was in possession of such agents or of this claimed embodiment.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy J. Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Scott D. Priebe
Primary Examiner
Art Unit 1632